CYTOSKELETAL DISRUPTION RESULTING FROM EXCITOTOXIC INSULT AND IMPAIRED ENERGY METABOLISM: IMPLICATIONS FOR ALZHEIMER'S DISEASE. J. Geddes, V. Bondada and Z. Pang, Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA.

Neurofibrillary tangles (NFTs), a hallmark of Alzheimer's disease neuropathology, reflect a massive disruption of the neuronal cytoskeleton which includes the somatodendritic accumulation of hyperphosphorylated tau and the loss of MAP2, neurofilaments, and other cytoskeletal proteins. The abundance of NFTs in regions with a high density of NMDA receptors suggests the possible involvement of excitotoxic mechanisms. Moreover, impaired energy metabolism can result in excitotoxic neuronal death and is proposed to contribute to several late-onset neurodegenerative disorders including AD.

To determine if excitotoxic insult and impaired energy metabolism might play a causal role in the formation of neurofibrillary pathology, we have examined the effects of metabolic poisons and excitotoxins on the neuronal cytoskeleton. Intrahippocampal injection of excitotoxins (i.e. quinolinate) results in neuronal death, loss of dendritic MAP2, but sparing of axonal tau. Mitochondrial poisons such as 3-nitropropionic acid and malonic acid produce a similar pattern of cytoskeletal disruption and neuronal loss. The results support the hypothesis that metabolic inhibition and excitotoxic insult may contribute to the sparing of tau and loss of other cytoskeletal proteins in tangle-bearing neurons in AD.